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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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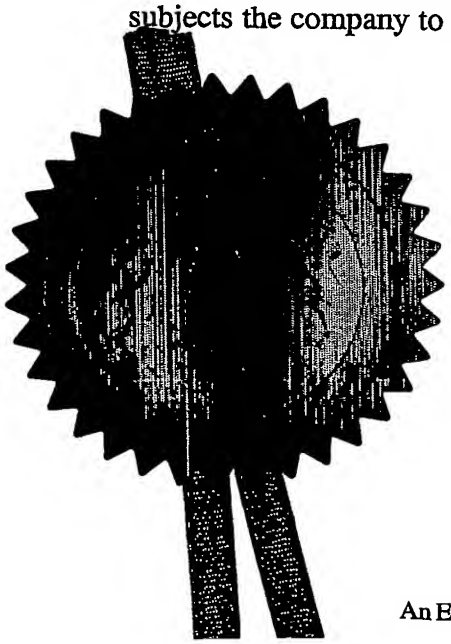

Signed Andrew Guy

Dated 16 February 2004

Patents Form 1/77

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12JUN03 E814284-1 D00624
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Request for grant of a patent

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1.	Your reference	4-33226P1/HO 80
2.	Patent application number *(The Patent Office will fill in this part)*	0313489.7 — 11 JUN 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic Compounds
	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH 1800001

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	26
Claim(s)	4
Abstract	
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B.A. Yorke & Co. Date 11th June 2003

12. Name and daytime telephone number of person to contact in the United Kingdom Mrs. S. Schnerr 020 8560 5847

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Notes

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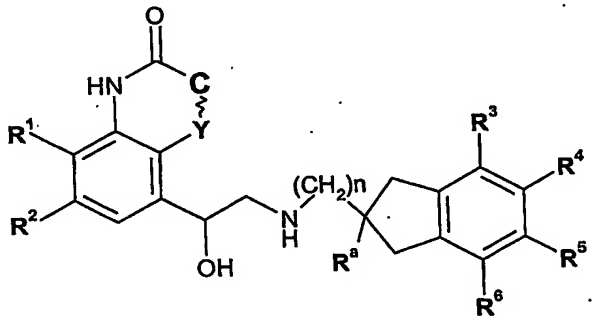
ORGANIC COMPOUNDS

This invention relates to organic compounds, their preparation and use as pharmaceuticals.

The invention provides in one aspect a compound of formula I



I

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

R^a is C_1-C_{10}-alkyl substituted by C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy, a C_5-C_{15}-carbocyclic group or by a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur; and

R^3, R^4, R^5 and R^6 are independently hydrogen, halo, cyano, carboxy, nitro, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy, tri-C_1-C_{10}-alkylsilyl, aminocarbonyl, amino, C_1-C_{10}-alkylamino, di(C_1-C_{10}-alkyl)amino, a C_5-C_{15}-carbocyclic group or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur,

or any two of R^3, R^4, R^5 and R^6 that are attached to adjacent carbon atoms on the benzene ring together with the carbon atoms to which they are attached form a C_3-C_{10}-cycloalliphatic ring, a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, or a benzene ring optionally substituted by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl.

Terms used in this specification have the following meanings:

"Substituted" as used herein means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

"C_1-C_{10}-alkyl" as used herein denotes straight chain or branched alkyl, which may be, for example, C_1 to C_{10} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, or straight or branched pentyl, hexyl, heptyl, octyl, nonyl or decyl. Preferably C_1-C_{10}-alkyl is C_1-C_4-alkyl.

"C_3-C_{10}-cycloalkyl" as used herein denotes cycloalkyl having 3 to 10 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Preferably C_3-C_{10}-cycloalkyl is C_3-C_6-cycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

"C_1-C_8-alkylene" as used herein denotes straight chain or branched alkylene, which may be, for example, C_1 to C_{10} alkylene such as methylene, ethylene, n-propylene, isopropylene, n-butylene, isobutylene, sec-butylene, tert-butylene, or straight or branched pentylene, hexylene, heptylene, octylene, nonylene or decylene. Preferably C_1-C_{10}-alkylene is C_1-C_4-alkylene.

"C_2-C_{10}-alkenyl" as used herein denotes straight chain or branched hydrocarbon chains that contain 2 to 10 carbon atoms and one or more carbon-carbon double bonds, for example, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, tert-butenyl, or straight or branched pentenyl, hexenyl, heptenyl, octenyl, nonenyl or decenyl. Preferably "C_2-C_{10}-alkenyl" is "C_2-C_4-alkenyl".

"C_3-C_{10}-cycloalkenyl" as used herein denotes a monovalent hydrocarbon cyclic group that contains 3 to 10 ring carbon atoms and at least one but no more than two carbon-carbon double bonds, for example a monocyclic group such as a cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl or cyclodecenyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicyclohexenyl, bicycloheptenyl, bicyclooctenyl, bicyclononenyl or bicyclodecenyl. Preferably C_3-C_{10}-cycloalkenyl is C_3-C_6-cycloalkenyl, for example cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

"C_1-C_{10}-alkoxy" as used herein denotes straight chain or branched alkoxy, which may be, for example, C_1 to C_{10} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy,

isobutoxy, sec-butoxy, tert-butoxy, or straight or branched pentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy or decyloxy. Preferably C_1-C_{10}-alkoxy is C_1-C_6-alkoxy.

"C_6-C_{10}-aryl" as used herein denotes a monovalent carbocyclic aromatic group that contains 6 to 10 carbon atoms and which may be, for example, a monocyclic group such as phenyl or a bicyclic group such as naphthyl. Preferably C_6-C_{10}-aryl is C_6-C_8-aryl, especially phenyl.

"C_7-C_{15}-aralkyl" as used herein denotes alkyl, for example C_1-C_5-alkyl as hereinbefore defined, substituted by C_6-C_{10}-aryl as hereinbefore defined. Preferably C_7-C_{15}-aralkyl is C_7-C_{10}-aralkyl such as phenyl-C_1-C_4-alkyl.

"C_7-C_{15}-aralkylene" as used herein denotes alkylene, for example C_1-C_5-alkylene as hereinbefore defined, substituted by C_6-C_{10}-aryl as hereinbefore defined. Preferably C_7-C_{15}-aralkylene is C_7-C_{10}-aralkylene such as phenyl-C_1-C_4-alkylene.

"C_7-C_{15}-aralkyloxy" as used herein denotes alkoxy, for example C_1-C_5-alkoxy as hereinbefore defined, substituted by C_6-C_{10}-aryl as hereinbefore defined. Preferably C_7-C_{15}-aralkyloxy is C_7-C_{10}-aralkyloxy such as phenyl-C_1-C_4-alkoxy, particularly benzyloxy.

"C_5-C_{15}-carbocyclic group" as used herein denotes a carbocyclic group having 5 to 15 ring carbon atoms, for example a monocyclic group, either aromatic or non-aromatic, such as a cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or phenyl, or a bicyclic group such as bicyclooctyl, bicyclononyl, bicyclodecyl, indanyl or indenyl, again any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups. Preferably the C_5-C_{15}-carbocyclic group is a C_5-C_{10}-carbocyclic group, especially phenyl. The C_5-C_{15}-carbocyclic group can substituted can be unsubstituted or substituted. Preferred substituents on the heterocyclic ring include halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy and C_3-C_{10}-cycloalkyl. When the C_5-C_{15}-carbocyclic group is phenyl it is most preferably unsubstituted or substituted by either C_1-C_{10}-alkyl especially methyl or C_1-C_4-alkoxy especially methoxy.

"C_3-C_{10}-cycloaliphatic ring" as used herein denotes a cycloaliphatic ring having 3 to 10 ring carbon atoms, for example a C_3-C_{10}-cycloalkyl as hereinbefore defined or a C_3-C_{10}-cycloalkenyl".

"5- or 6- membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur" as used herein may be, for example, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, tetrazole, furan, thiadiazole, thiazole, isothiazole, thiophene, oxadiazole, pyridine, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperazine, morpholino, triazine, oxazine or thiazole. Preferred 5- or 6-membered heterocyclic rings include furan, thiazole and pyridine. The 5- or 6- membered heterocyclic ring can be unsubstituted or substituted. Preferred substituents on the heterocyclic ring include halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy and C_3-C_{10}-cycloalkyl. When the 5- or 6- membered heterocyclic ring is a substituent on the benzo ring of the indanyl group of the compound of formula I it is preferably unsubstituted pyridyl or it is furanyl or thiazolyl substituted by either halo or C_1-C_4-alkyl.

When any two of R^3, R^4, R^5 and R^6 that are attached to adjacent carbon atoms on the benzene ring together with the carbon atoms to which they are attached form a benzene ring. The benzene ring so formed can be unsubstituted or substituted. Preferred substituents on that ring include halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy and C_3-C_{10}-cycloalkyl.

"Halo" or "halogen" as used herein denotes a element belonging to group 17 (formerly group VII) of the Periodic Table of Elements, which may be, for example, fluorine, chlorine, bromine or iodine. Preferably halo or halogen is fluorine, chlorine or bromine, but especially chlorine.

"Halo-C_1-C_{10}-alkyl" as used herein denotes C_1-C_{10}-alkyl as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms. Preferably halo-C_1-C_{10}-alkyl is fluoro-C_1-C_{10}-alkyl, especially trifluoromethyl.

"Tri-C_1-C_{10}-alkylsilyl" as used herein denotes silyl substituted by three C_1-C_{10}-alkyl groups as hereinbefore defined.

"Aminocarbonyl" as used herein denotes amino attached through the nitrogen atom to a carbonyl group.

"C_1-C_{10}-alkylamino" and "di(C_1-C_{10}-alkyl)amino" as used herein denote amino substituted respectively by one or two C_1-C_{10}-alkyl groups as hereinbefore defined, which may be the same or different. Preferably C_1-C_{10}-alkylamino and di(C_1-C_{10}-alkyl)amino are respectively C_1-C_4-alkylamino and di(C_1-C_4-alkyl)amino.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Preferred compounds of the present invention are compounds of formula I where
-C~Y- is -CH=CH-;
one of R^1 and R^2 is hydroxy and the other is hydrogen;
n is 0;
R^a is C_1-C_{10}-alkyl substituted by C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy or by a C_5-C_{15}-carbocyclic group; and
R^3, R^4, R^5 and R^6 are independently hydrogen or C_1-C_{10}-alkyl.

Especially preferred compounds of the present invention are compounds of formula I where
-C~Y- is -CH=CH-;
one of R^1 and R^2 is hydroxy and the other is hydrogen;
n is 0;
R^a is C_1-C_{14}-alkyl substituted by C_1-C_6-alkoxy, C_7-C_{10}-aralkyloxy or by a C_5-C_{10}-carbocyclic group; and
R^3 and R^6 are both hydrogen; and
R^4 and R^5 are independently hydrogen or C_1-C_4-alkyl.

The compounds of formula (I) are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propionic acid, butyric acid, benzoic acid, o-hydroxybenzoic acid, p-hydroxybenzoic acid, p-chlorobenzoic acid, diphenylacetic acid, triphenylacetic acid, 1-hydroxynaphthalene-2-carboxylic acid, 3-hydroxynaphthalene-2-carboxylic acid, aliphatic hydroxy acids such as

lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as fumaric acid, maleic acid or succinic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

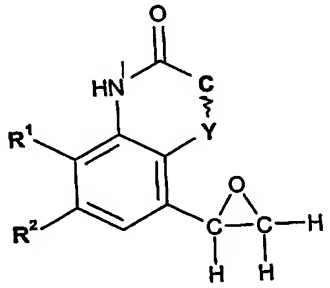
Compounds of formula I which contain acidic e.g. carboxyl groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of formula I by known salt-forming procedures.

In those compounds where there is an asymmetric carbon atom the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The present invention embraces individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

Specific especially preferred compounds of the invention are those described hereinafter in the Examples.

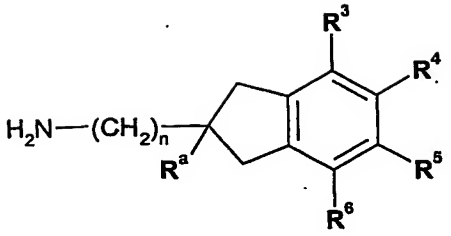
The present invention also provides a process for the preparation of compounds of formula I in free or salt or solvate form. They can be prepared by a process comprising:

(i) (A) for the preparation of compounds of formula I reacting a compound of formula II



II

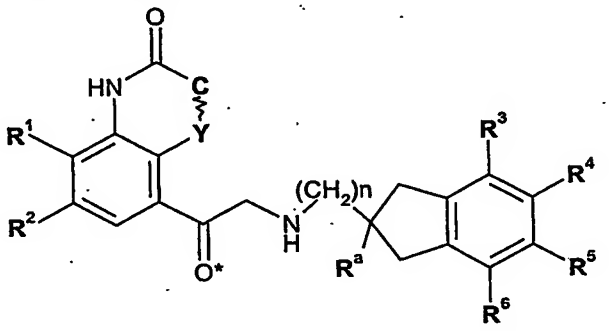
or a protected form thereof wherein -C~Y-, R^1 and R^2 are as defined in claim 1, with a compound of formula III



III

or a protected form thereof wherein R^a, R^3, R^4, R^5, R^6 and n are as hereinbefore defined; or

(B) reducing a compound of formula IV



IV

or a protected form thereof wherein -C~Y-, R^a, R^1, R^2, R^3, R^4, R^5, R^6 and n are as hereinbefore defined, to convert the indicated keto group into -CH(OH); and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

Process variant (A) may be carried out using known procedures for reacting epoxides with amines or analogously as hereinafter described in the Examples. The reaction is conveniently carried out without a solvent or in an inert solvent, for example an organic solvent such as 2-methoxyethyl ether. The reaction temperature is conveniently from 25°C to 200°C, preferably from 80°C to 190°C. The temperature may be achieved by conventional heating or by microwave irradiation.

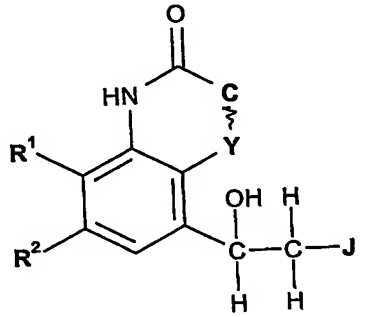
Process variant (B) may be carried out using conventional methods, for example by hydrogenation using a suitable catalyst such as Pd/C or by reaction with sodium borohydride or a borane reducing agent under conventional conditions.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I

can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula II are known compounds or can be prepared by processes analogous to those used for the preparation of the known compounds, for example the procedures described in J. Med. Chem. 1987, 30, 1563.

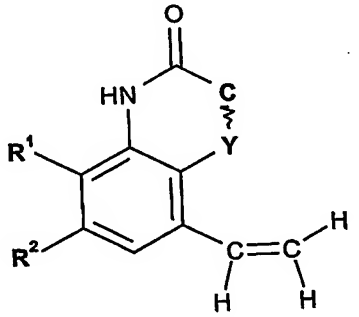
Compounds of formula II in which the carbon atom of the epoxide ring that is attached to the phenyl group is chiral may be prepared from a compound of formula V



V

or a protected form thereof where -C~Y-, R^1 and R^2 are as hereinbefore defined and J is a leaving atom or group, as described in international patent application WO 95/25104 or analogously as hereinafter described in the Examples.

Compounds of formula II may alternatively be prepared by epoxidation of a compound of formula VI

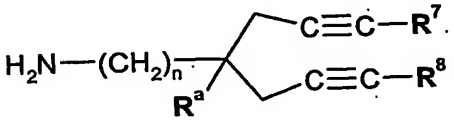


VI

or a protected form thereof -C~Y-, R^1 and R^2 are as hereinbefore defined, using conventional procedures.

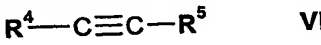
Compounds of formula III are known or may be prepared by methods analogous to those used for the preparation of the known compounds. The amine group may be protected by known methods.

Compounds of formula III where R^3 and R^6 are hydrogen can be prepared by reacting a compound of formula VII



VII

where R^a and n are as hereinbefore defined and R^7 and R^8 are each independently hydrogen or C_1-C_{10}-alkyl, with a compound of formula VIII

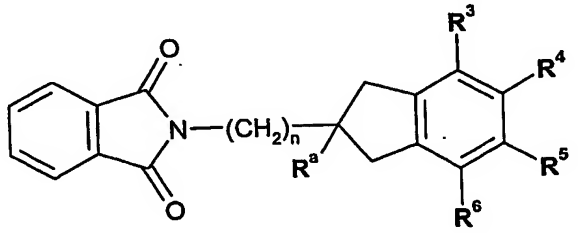


VIII

where R^4 and R^5 are as hereinbefore defined. The reaction may be carried out using known procedures, for example as described in international patent application WO 96/23760 or analogously as hereinafter described in the Examples. The reaction is conveniently carried out in an inert solvent, for example ethanol, preferably in the presence of a catalyst such as tris(triphenylphosphine)rhodium chloride. The reaction temperature is conveniently from 60 to 120°C, preferably from 80 to 100°C. Where R^4 and R^5 are trialkylsilyl, the reaction between the compounds of formulae IX and X may be carried out in the presence of a metal carbonyl complex catalyst, for example using the procedure described by K.P.C. Vollhardt and R. Hillard, *J. Am. Chem. Soc.* 1977, 99, 4058.

Compounds of formula III where n is 0 may be prepared by amination of the corresponding 2-alkyl-indan-1-one using ammonia and potassium hexacyanoferrate ($K_3Fe(CN)_6$), for example using the procedure described in Farnum and Carlson, *Synthesis* 1972, 191, followed by reduction of the keto group or analogously as hereinafter described in the Examples.

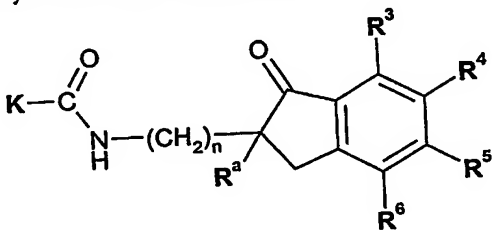
Compounds of formula III where R^a is C_1-C_{10}-alkyl substituted by C_1-C_{10}-alkoxy or C_7-C_{15}-aralkyloxy may be prepared by deprotecting a compound of formula IX



IX

where R^a, R^3, R^4, R^5, R^6 and n are as hereinbefore defined. The reaction may be carried out using conventional procedures, for example by refluxing hydrazine hydrate in an organic solvent such as ethanol, or analogously as hereinafter described in the Examples.

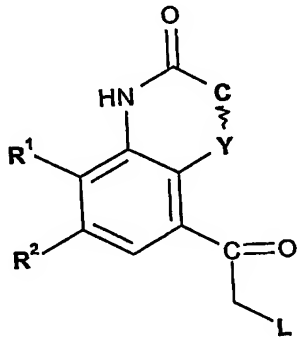
Compounds of formula III where R^a is C_1-C_{10}-alkyl substituted by a C_5-C_{15}-carbocyclic group may be prepared by reducing a compound of formula X



X

where R^a, R^3, R^4, R^5, R^6 and n are as hereinbefore defined and K is a halo-C_1-C_8-alkyl, especially, for example trifluoromethyl. The reaction may be carried out using known procedures, for example using the procedure described in "Advanced Organic Chemistry", J. March, Wiley, 4th edition 1992, page 1209, or analogously as hereinafter described in the Examples.

Compounds of formula IV are novel compounds which may be prepared by reaction of a compound of formula XI



XI

or a protected form thereof where -C~Y-, R^1 and R^2 are as hereinbefore defined and L is a halogen atom, preferably chlorine or bromine, with a compound of formula III as hereinbefore defined. The reaction may be carried out using known procedures, for example those described by Yoshizaki et al, *J. Med. Chem.* 1976, 19, 1138, or analogously as hereinafter described in the Examples.

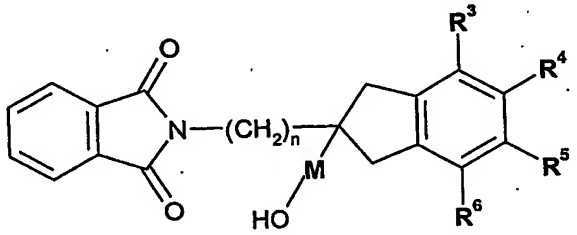
Compounds of formula V are known or may be prepared by methods analogous to those used for the preparation of known compounds, for example those used in the Examples hereinafter.

Compounds of formula VI are known or may be prepared by known procedures.

Compounds of formula VII may be prepared as described in international patent application WO 96/23760 or by analogous procedures.

Compounds of formula VIII are known or may be prepared by known procedures.

Compounds of formula IX may be prepared by reacting a compound of formula XII



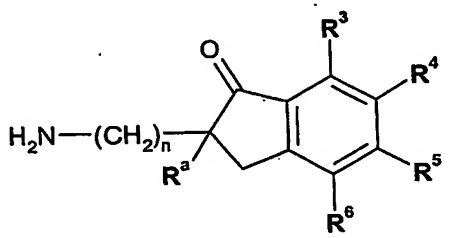
XII

where R^a, R^3, R^4, R^5, R^6 and n are as hereinbefore defined and M is C_1-C_{10}-alkylene, with a compound of formula XIII

XIII

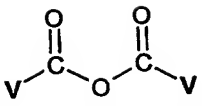
or protected form thereof where T is C_1-C_{10}-alkyl/C_1-C_{10}-alkylene or C_7-C_{15}-aralkyl/C_7-C_{15}-aralkylene and U is a leaving atom or group. The reaction may be carried out using known methods for converting hydroxyl groups to alkoxy or aralkyloxy groups. For example a compound of formula XII may be conveniently reacted with diazomethane or a diazomethane equivalent such as (trimethylsilyl)diazomethane using the procedure described in *Tet. Lett.* 1990, vol. 31, 5507 to give a compound of formula IX where R^a is C_1-C_8-alkylene substituted by methoxy. The reaction is conveniently carried out in an organic solvent, for example dichloromethane, preferably in the presence of a strong acid such as fluoroboric acid or analogously as hereinafter described in the Examples. The reaction temperature is conveniently from -10 to 10°C, but preferably about 0°C.

Compounds of formula X may be prepared by reacting a compound of formula XIV



XIV

where R^a, R^3, R^4, R^5, R^6 and n are as hereinbefore defined, with a compound of formula XV

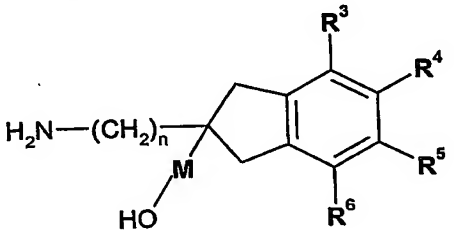


XV

where each V is a halo-C_1-C_8-alkyl, especially for example in both cases trifluoromethyl (i.e. giving trifluoroacetic anhydride). The reaction may be carried out using known procedures for reacting primary amines with anhydrides or analogously as hereinafter described in the Examples. The reaction is conveniently carried out in an organic solvent, for example tetrahydrofuran, preferably in the presence of a base such as triethylamine. The reaction temperature is conveniently from 10 to 60°C, but preferably room temperature.

Compounds of formula XI are known or may be prepared by known procedures, for example those disclosed in United States patent specification US 4460581 and German patent specification DE 3134590.

Compounds of formula XII may be prepared by reacting a compound of formula XVI

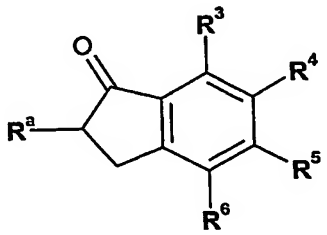


XVI

where R^3, R^4, R^5, R^6 and n are as hereinbefore defined and M is C_1-C_{10}-alkylene, with phthalic anhydride. The reaction may be carried out using known procedures for reacting amines with phthalic anhydride or analogously as hereinafter described in the Examples. The reaction can be carried out in an organic solvent but it is preferably carried out using neat phthalic anhydride. The reaction temperature is conveniently from 120 to 200°C, but preferably about 200°C.

Compounds of formula XIII are known or may be prepared by known procedures.

Compounds of formula XIV are known or may be prepared by aminating a compound of formula XVII

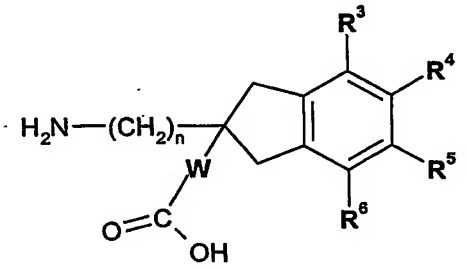


XVII

where R^a, R^3, R^4, R^5 and R^6 are as hereinbefore defined, for example using ammonia and potassium hexacyanoferrate $K_3Fe(CN)_6$ in the procedure described in Farnum and Carlson, *Synthesis* 1972, 191, or analogously as hereinafter described in the Examples. The reaction temperature is conveniently from 60 to 100°C, but preferably about 80°C.

Compounds of formula XV are known or may be prepared by known procedures.

Compounds of formula XVI are known or may be prepared by reducing a compound of formula XVIII



XVIII

where R^3, R^4, R^5 and R^6 are as hereinbefore defined and W is C_1-C_9-alkylene or a bond. The reaction may be carried out using known procedures for reducing carboxylic acids to give primary alcohols, for example using lithium aluminium hydride in ether as described in "Advanced Organic Chemistry", J. March, Wiley, 4th edition 1992, page 1212, or analogously as hereinafter described in the Examples. The reaction temperature is conveniently from 10 to 40°C, but preferably room temperature.

Compounds of formula XVII are known or may be prepared by known procedures, for example the procedure described in *J. Mol. Catal. A.* 2000, 154,237, or analogously as hereinafter described in the Examples.

Compounds of formula XVIII are known or may be prepared by known procedures, for example the procedure described in *J. Med. Chem.* 1991, 34, 3125, or analogously as hereinafter described in the Examples.

Where desired, the protection of any reactive group may be carried out at any appropriate stage in the above processes. The protecting group is suitably one used conventionally in the art such as preferably benzyl or trifluoroacetyl and may be introduced and removed using a conventional procedure, for example using an amine-protective group as described in Protective Groups in Organic Synthesis, T. W. Greene, P.G.M. Wuts, John Wiley & Sons Inc, Third Edition, 1999. When a hydroxy group is protected by a benzyl group, the latter

may be removed by catalytic hydrogenation in the presence of palladium on charcoal using conventional procedures, such as those used hereinafter in the Examples.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula I in free, salt or solvate form are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free, salt or solvate form for use as a pharmaceutical. The compounds of formula I in free, salt or solvate form, hereinafter referred to alternatively as "agents of the invention", have good β_2-adreno-receptor agonist activity. The β_2 agonist activity, onset of action and duration of action of the agents of the invention may be tested using the guinea pig tracheal strip in vitro assay according to the procedure of R.A. Coleman and A.T. Nials, *J. Pharmacol. Methods* 1989, 21, 71. The binding potency and selectivity for the β_2-adrenoreceptor relative to the β_1-adrenoreceptor can be measured by a classical filtration binding assay according to the procedure of Current Protocols in Pharmacology (S. J. Enna (editor-in-chief) et al, John Wiley & Son, Inc, 1998), or by cAMP determination in cells expressing β_2- or β_1-adrenoceptor, according to the procedure of B. January et al, *Brit. J. Pharmacol.* 1998, 123, 701.

The agents of the invention commonly have a rapid onset of action and have a prolonged stimulating action on the β_2-adrenoreceptor, compounds of the Examples hereinbelow having K_i (β_2) values of the order of 0.1 to 1000 nM, having durations of action of the order of 1 to greater than 12 hours. Many of the compounds have binding selectivities for the β_2-adrenoreceptor relative to the β_1-adrenoreceptor from 1.5 to 500. The compound of Example 1 has β_2 and β_1 binding potencies, measured by a classical filtration binding assay, represented by K_i values (β_2/β_1) (in μM) of 0.1278 / 0.3835.

Having regard to their β_2 agonist activity, the agents of the invention are suitable for use in the treatment of any condition which is prevented or alleviated by activation of the β_2-

adrenoreceptor. In view of their long acting selective β_2 agonist activity, the agents of the invention are useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. Relief of bronchoconstriction can be measured in models such as the in vivo plethysmography models of Chong et al, *J. Pharmacol. Toxicol. Methods* 1998, 39, 163, Hammelmann et al, *Am. J. Respir. Crit. Care Med.*, 1997, 156, 766 and analogous models. The agents of the invention are therefore useful in the treatment of obstructive or inflammatory airways diseases. In view of their long duration of action, it is possible to administer the agents of the invention once-a-day in the treatment of such diseases. In another aspect, agents of the invention commonly exhibit characteristics indicating a low incidence of side effects commonly encountered with β_2 agonists such as tachycardia, tremor and restlessness, such agents accordingly being suitable for use in on demand (rescue) treatment as well as prophylactic treatment of obstructive or inflammatory airways diseases.

Treatment of a disease in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

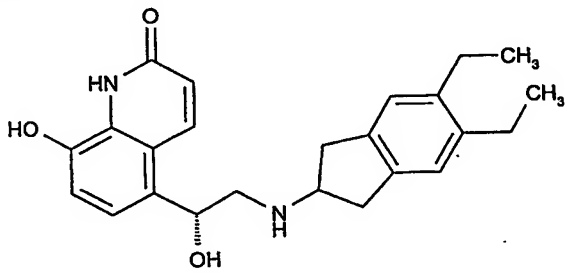
Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), including chronic bronchitis, or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their β_2 agonist activity, the agents of the invention are also useful in the treatment of a condition requiring relaxation of smooth muscle of the uterus or vascular system. They are thus useful for the prevention or alleviation of premature labour pains in pregnancy. They are also useful in the treatment of chronic and acute urticaria, psoriasis, allergic conjunctivitis, actinitis, hay fever, and mastocytosis.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical composition. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate and compounds described in WO 0200679, WO 0288167, WO 0212266 and WO 02100879, LTB4 antagonists such as those described

in US 5451700, LTB4 antagonists such as those described in US 5451700, LTD4 antagonists such as montelukast and zafirlukast, PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene) and KW-4490 (Kyowa Hakko Kogyo) and A2a agonists such as those described in EP 1052264, EP 1241176, WO 0023457, WO0077018, WO 0123399, WO 0160835, WO 0194368, WO 0200676, WO 0222630, WO 0296462, WO 0127130, WO 0127131, WO 9602543, WO 9602553, WO 9828319, WO 9924449, WO 9924450, WO 9924451, WO 9938877, WO 9941267, WO 9967263, WO 9967264, WO 9967265, WO 9967266, WO 9417090, EP 409595A2 and WO 0078774 and A2b antagonists such as those described in WO 02/42298. Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide, but also those described in EP 424021, US 5171744 (Pfizer) and WO 01/04118 (Almirall Prodesfarma).

The agents of the invention are also useful as co-therapeutic agents for use in combination other beta-2 adrenoceptor agonists, for example as a rescue medication. Suitable beta-2 adrenoceptor agonists include salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International patent publication No. WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof.

Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride.

Combinations of agents of the invention and steroids, PDE4 inhibitors, A2a agonists, A2b agonists or LTD4 antagonists may be used, for example, in the treatment of COPD or,

particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, A2a agonists, A2b agonists, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or inflammatory airways diseases.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula I in free form or in the form of a pharmaceutically acceptable salt or solvate thereof, optionally together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compound of formula I having a particle diameter up to 10 microns, optionally together with a diluent or

carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula I either dissolved, or suspended, in a vehicle containing water, a co-solvent such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

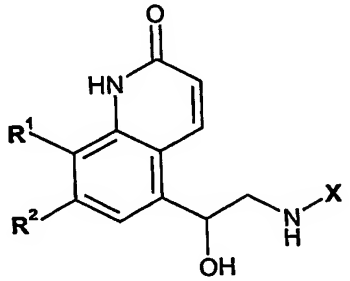
The invention also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

Dosages employed in practising the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of from 1 to 5000 μg.

The invention is illustrated by the following Examples.

Examples

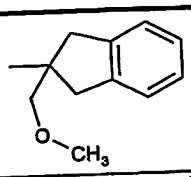
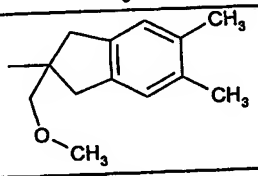
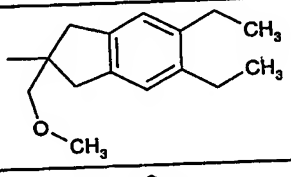
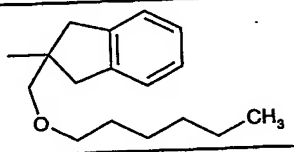
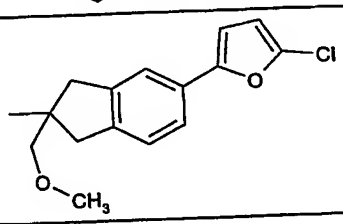
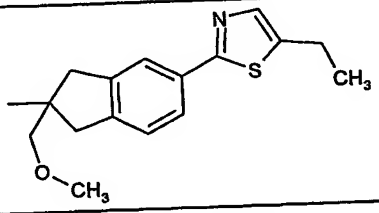
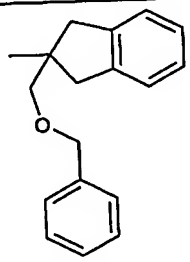
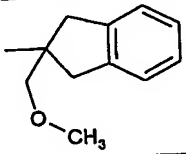
Especially preferred compounds of formula I are also compounds of formula XIX

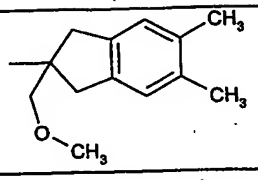
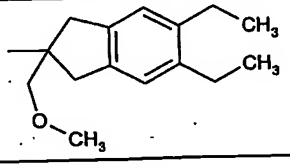
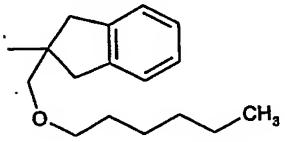
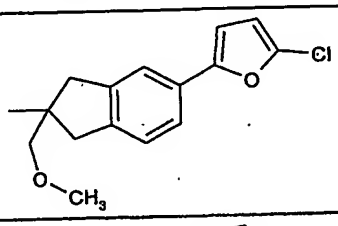
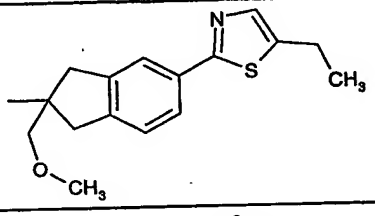
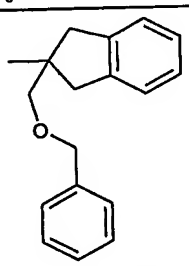
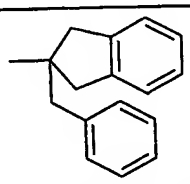
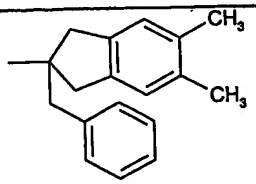
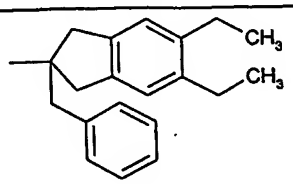


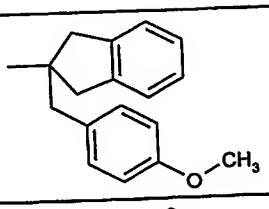
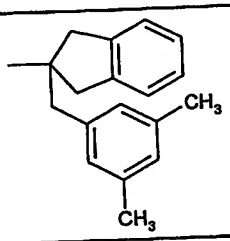
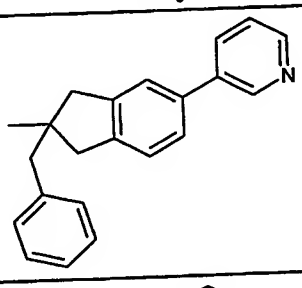
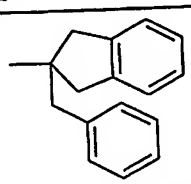
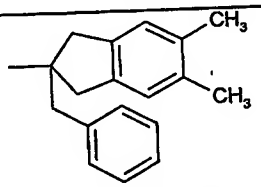
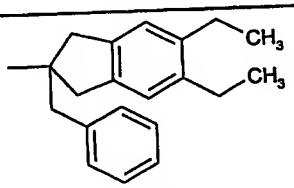
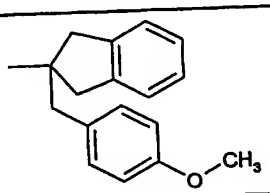
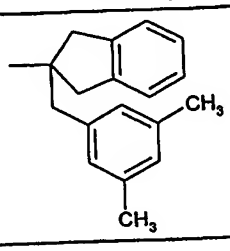
XIX

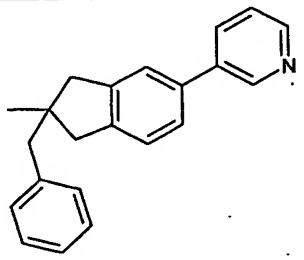
wherein X is as shown in the following table, the method of preparation being described hereinafter. The compound of Example 1 is prepared as a trifluoroacetate salt. 1H NMR spectra are recorded at 400 MHz in $CDCl_3$ unless otherwise noted. Mass spectra are

obtained under electrospray ionisation conditions with LC gradient elution of 5% to 95% acetonitrile-water in the presence of 0.1% formic acid.

Ex	R^1	R^2	X	MH^+
1	-OH	-H		381
2	-OH	-H		-
3	-OH	-H		-
4	-OH	-H		-
5	-OH	-H		-
6	-OH	-H		-
7	-OH	-H		-
8	-H	-OH		-

9	-H	-OH		-
10	-H	-OH		-
11	-H	-OH		-
12	-H	-OH		-
13	-H	-OH		-
14	-H	-OH		-
15	-OH	-H		-
16	-OH	-H		-
17	-OH	-H		-

18	-OH	-H		-
19	-OH	-H		-
20	-OH	-H		-
21	-H	-OH		-
22	-H	-OH		-
23	-H	-OH		-
24	-H	-OH		-
25	-H	-OH		-

26	-H	-OH		-

Example 1

8-Hydroxy-5-[*R*-1-hydroxy-2-(2-methoxymethylindan-2-ylamino)-ethyl]-1H-quinolin-2-one

Lithium aluminium hydride (1 M solution in ether, 23.7 ml, 23.7 mmol) is added to a solution of 2-aminoindan-2-carboxylic acid (*J. Med. Chem.* 1991, 34, 3125; 2.26 g, 12.8 mmol) in ether (150 ml). The reaction is stirred for 2 hours at ambient temperature and quenched sequentially with water (0.9 ml), 2 M NaOH (0.9 ml) and further water (0.9 ml). $MgSO_4$ is added and the resultant suspension is filtered. The filtrate is evaporated to afford (2-aminoindan-2-yl)methanol, MH+ 164.

A mixture of (2-aminoindan-2-yl)methanol (0.407 g, 2.50 mmol) and phthalic anhydride (0.369 g, 2.50 mmol) is heated at 160°C for 40 minutes. The reaction mixture is poured into water and extracted with chloroform. The organic phase is dried (Na_2SO_4) and evaporated to afford 2-(2-hydroxymethylindan-2-yl)-isoindole-1,3-dione, MH+ 294.

(Trimethylsilyl)diazomethane (2 M hexanes, 0.51 ml, 1.03 mmol) is added dropwise to a cooled (0°C) solution of 2-(2-hydroxymethylindan-2-yl)-isoindole-1,3-dione (0.150 g, 0.511 mmol) and fluoroboric acid (48% aqueous, 93.5 µl, 0.511 mmol) in CH_2Cl_2 (4 ml). The reaction is stirred for 20 minutes, then three further portions of (trimethylsilyl)diazomethane (2 M hexanes, 0.128 ml, 0.25 mmol; 64 µl, 0.12 mol; 64 µl, 0.12 mmol)) are made at 20 minute intervals. The reaction is stirred for a further 40 minutes after the final addition, poured into water and extracted with dichloromethane. The organic phase is washed with brine, dried ($MgSO_4$) and evaporated. The crude product is purified by flash chromatography (CH_2Cl_2 elution) to afford 2-(2-methoxymethylindan-2-yl)-isoindole-1,3-dione, MH+ 308.

A mixture of 2-(2-methoxymethylindan-2-yl)-isoindole-1,3-dione (0.30 g, 0.976 mmol) and hydrazine hydrate (47 µl, 0.976 mmol) in 95% ethanol (15 ml) is heated to reflux for 45 hours. Further hydrazine hydrate (9.4 µl, 0.976 mmol) is added and the reaction refluxed

for an additional 16 hours, followed by addition of a final portion of hydrazine hydrate (9.4 µl, 0.976 mmol) and a further 16 hours reflux. After cooling, the resultant suspension is filtered and the filter cake washed with ethanol. The combined filtrate and washings are evaporated and triturated with ether to afford 2-methoxymethylindan-2-ylamine, MH+ 178.

A mixture of 2-methoxymethylindan-2-ylamine (0.140 g, 0.790 mmol) and 8-benzyloxy-5-*R*-oxiranyl-1H-quinolin-2-one (0.154 g, 0.527 mmol) in 2-methoxyethyl ether (2.5 ml) is degassed by bubbling argon for 5 minutes then heated in a sealed tube at 190°C for 60 hours. The solvent is evaporated and the crude product purified by flash chromatography (20:1 CH_2Cl_2/MeOH elution) to afford 8-benzyloxy-5-[*R*-1-hydroxy-2-(2-methoxymethylindan-2-ylamino)-ethyl]-1H-quinolin-2-one, MH+ 471.

A mixture of 8-benzyloxy-5-[*R*-1-hydroxy-2-(2-methoxymethylindan-2-ylamino)-ethyl]-1H-quinolin-2-one (50 mg, 0.106 mmol) and 10% Pd/C (19 mg) in ethanol (5 ml) is hydrogenated at 0.35 bar for 4 hours. The reaction mixture is filtered and the filtrate evaporated. The residue is purified by preparative HPLC to afford 8-hydroxy-5-[*R*-1-hydroxy-2-(2-methoxymethylindan-2-ylamino)-ethyl]-1H-quinolin-2-one trifluoroacetate, MH+ 381.

Examples 2 to 7

The compounds of these Examples are prepared analogously to Example 1.

Examples 8 to 14

The compounds of these Examples are prepared using procedures that are analogous to those described in Example 1 except using 7- benzyloxy-5-*R*-oxiranyl-3,4-dihydro-1H-quinolin-2-one in place of 8-benzyloxy-5-*R*-oxiranyl-1H-quinolin-2-one.

Example 15

5-[*R*-2-(2-Benzylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one

$K_3Fe(CN)_6$ (18.0 g, 54.8 mmol) is added to hot (80°C) degassed water (150 ml), followed by 2-benzylindan-1-one (*J. Mol. Catal. A* 2000, 154, 237; 3.8 g, 17.1 mmol). Concentrated aqueous ammonia (14 ml) is then added over 15 minutes and the reaction mixture heated at 80-90°C in the dark for 24 hr. After cooling to ambient temperature, the mixture is extracted with chloroform. The combined chloroform extracts are extracted with 3 M HCl

and the acidic extracts are evaporated to afford 2-amino-2-benzylindan-1-one hydrochloride, MH+ 238.

Trifluoroacetic anhydride (0.763 ml, 5.4 mmol) is added to a cooled (0°C) solution of 2-amino-2-benzylindan-1-one hydrochloride (1.0 g, 3.65 mmol) and triethylamine (1.27 ml, 9.13 mmol) in tetrahydrofuran (THF) (50ml). The cooling bath is removed and the reaction is stirred at ambient temperature for 4 hours. Additional trifluoroacetic anhydride (0.102 ml, 0.73 mmol) is added and the reaction stirred for 16 hours. The solvent is evaporated and the residue partitioned between ether and 1 M HCl. The organic phase is washed with brine, dried ($MgSO_4$) and evaporated to afford N-(2-benzyl-1-oxoindan-2-yl)-2,2,2-trifluoro-acetamide, MH+ 334.

A mixture of N-(2-benzyl-1-oxoindan-2-yl)-2,2,2-trifluoroacetamide (0.200 g, 0.60 mmol), 10% Pd/C (50 mg) and concentrated H_2SO_4 (30 µl) in acetic acid (13.3 ml) is hydrogenated at 0.35 bar for 1 hr. Further concentrated H_2SO_4 (10 µl) is added and the hydrogenation continued for 16 hours. The reaction is filtered, the filtrate is evaporated and the residue partitioned between ethyl acetate and water. The aqueous phase is basified to pH 11 with 1 M aqueous NaOH and extracted with ethyl acetate. The organic extract is washed with brine, dried ($MgSO_4$) and evaporated to afford 2-benzylindan-2-ylamine, MH+ 224.

A mixture of 2-benzylindan-2-ylamine (55 mg, 0.246 mmol) and 8-benzyloxy-5-*R*-oxiranyl-1H-quinolin-2-one (48 mg, 0.164 mmol) in 2-methoxyethyl ether (2 ml) is degassed by bubbling argon for 5 minutes then heated in a sealed tube at 190°C for 40 hours. The solvent is evaporated and the crude product purified by flash chromatography (25:1 CH_2Cl_2/MeOH elution) to afford 5-[*R*-2-(2-benzylindan-2-ylamino)-1-hydroxyethyl]-8-benzyloxy-1H-quinolin-2-one, MH+ 517.

A mixture of 5-[*R*-2-(2-benzylindan-2-ylamino)-1-hydroxyethyl]-8-benzyloxy-1H-quinolin-2-one (22 mg, 0.04 mmol) and 10% Pd/C (10 mg) in ethanol (7 ml) is hydrogenated at 0.35 bar for 9 hours. The reaction mixture is filtered and the filtrate evaporated to afford 5-[(R)-2-(2-benzylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one, MH+ 427.

Examples 16 to and 20

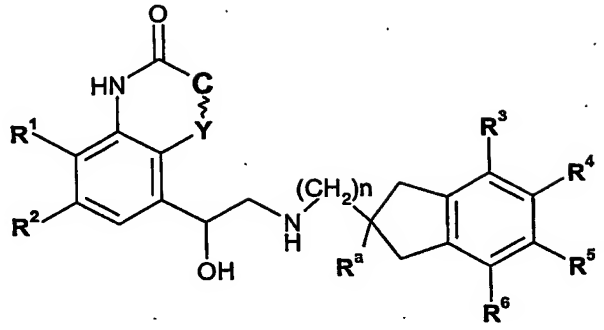
These compounds are prepared analogously to Example 15.

Examples 21 to 26

The compounds of these Examples are prepared using procedures that are analogous to those described in Example 15 except using 7- benzyloxy-5-*R*-oxiranyl-3,4-dihydro-1H-quinolin-2-one in place of 8-benzyloxy-5-*R*-oxiranyl-1H-quinolin-2-one.

CLAIMS

1. A compound of formula I



I

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

R^a is C_1-C_{10}-alkyl substituted by C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy, a C_5-C_{15}-carbocyclic group or by a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur; and

R^3, R^4, R^5 and R^6 are independently hydrogen, halo, cyano, carboxy, nitro, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy, tri-C_1-C_{10}-alkylsilyl, aminocarbonyl, amino, C_1-C_{10}-alkylamino, di(C_1-C_{10}-alkyl)amino, a C_5-C_{15}-carbocyclic group or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur,

or any two of R^3, R^4, R^5 and R^6 that are attached to adjacent carbon atoms on the benzene ring together with the carbon atoms to which they are attached form a C_3-C_{10}-cycloalliphatic ring, a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, or a benzene ring optionally substituted by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl.

2. A compound according to claim 1, where

-C~Y- is -CH=CH-;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is 0;

R^a is C_1-C_{10}-alkyl substituted by C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy or by a C_5-C_{15}-carbocyclic group; and

R^3, R^4, R^5 and R^6 are independently hydrogen or C_1-C_{10}-alkyl.

3. A compound according to claim 2, where

-C~Y- is -CH=CH-;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is 0;

R^a is C_1-C_{14}-alkyl substituted by C_1-C_6-alkoxy, C_7-C_{10}-aralkyloxy or by a C_5-C_{10}-carbocyclic group; and

R^3 and R^6 are both hydrogen; and

R^4 and R^5 are independently hydrogen or C_1-C_4-alkyl.

4. A compound according to claim 1 substantially as herein described with reference to any one of the Examples.

5. A compound according to any one of the preceding claims for use as a pharmaceutical.

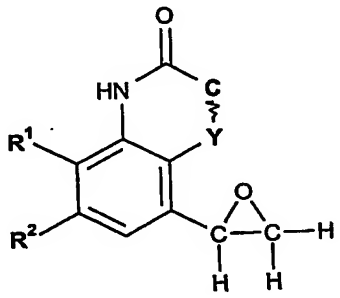
6. A pharmaceutical composition comprising a compound according to any one of the preceding claims, optionally together with a pharmaceutically acceptable carrier.

7. Use of a compound according to any one of claims 1 to 4 for the preparation of a medicament for the treatment of a condition which is prevented or alleviated by activation of the β_2-adrenoreceptor.

8. Use of a compound according to any one of claims 1 to 4 for the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

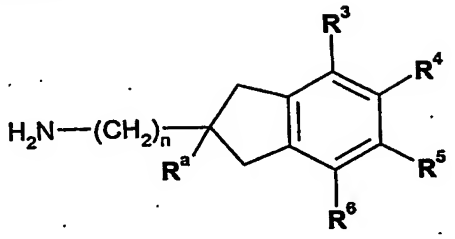
9. A process for the preparation of a compound of formula I as claimed in claim 1 in free or salt or solvate form comprising:

(i) (A) for the preparation of compounds of formula I reacting a compound of formula II



II

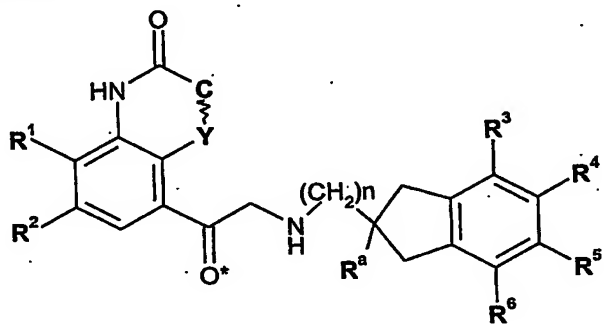
or a protected form thereof wherein -C-Y-, R^1 and R^2 are as defined in claim 1, with a compound of formula III



III

or a protected form thereof wherein R^a, R^3, R^4, R^5, R^6 and n are as defined in claim 1; or

(B) reducing a compound of formula IV

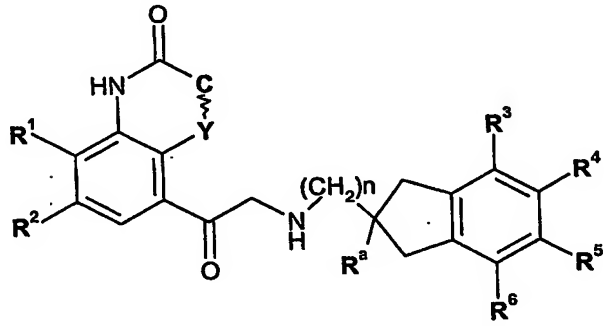


IV

or a protected form thereof wherein -C~Y-, R^a, R^1, R^2, R^3, R^4, R^5, R^6 and n are as defined in claim 1, to convert the indicated keto group into -CH(OH); and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

10. A compound of formula IV



IV

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

R^a is C_1-C_{10}-alkyl substituted by C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy, a C_5-C_{15}-carbocyclic group or by a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur; and

R^3, R^4, R^5 and R^6 are independently hydrogen, halo, cyano, carboxy, nitro, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy, tri-C_1-C_{10}-alkylsilyl, aminocarbonyl, amino, C_1-C_{10}-alkylamino, di(C_1-C_{10}-alkyl)amino, a C_5-C_{15}-carbocyclic group or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur,

or any two of R^3, R^4, R^5 and R^6 that are attached to adjacent carbon atoms on the benzene ring together with the carbon atoms to which they are attached form a C_3-C_{10}-cycloalliphatic ring, a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, or a benzene ring optionally substituted by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl.